

SMALL MOLECULE INHIBITORS OF DRUG RESISTANT FORMS OF HIV-1 INTEGRASE

SUMMARY

Researchers at the National Cancer Institute discovered small-molecule compounds containing 1-hydroxy-2-oxo-1,8-naphthyridine moieties whose activity against HIV-1 integrase mutants confer resistance to currently approved INSTIs. Preliminary rodent efficacy, metabolic, and pharmacokinetic studies have been completed by the NCI researchers. The National Cancer Institute seeks partners to commercialize this class of compounds through licensing or co-development.

REFERENCE NUMBER

E-093-2013

PRODUCT TYPE

- Therapeutics

KEYWORDS

- HIV therapy, integrase, strand transfer, drug resistant HIV
- raltegravir, elvitegravir, dolutegravir

COLLABORATION OPPORTUNITY

This invention is available for licensing and co-development.

CONTACT

John D. Hewes
NCI - National Cancer Institute
240-276-5515

John.Hewes@nih.gov

DESCRIPTION OF TECHNOLOGY

Integrase strand transfer inhibitors ("INSTIs") are currently in use as a component of prophylactic antiretroviral therapy for preventing HIV-1 infection from progressing to AIDS. Three INSTIs are approved by the FDA for inclusion in antiretroviral regimens: raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG). Clinicians have already identified several HIV-1 integrase mutations that confer resistance to RAL and EVG, and additional mutations that confer resistance to all three INSTIs has been identified in the laboratory.

Researchers at the National Cancer Institute discovered small-molecule compounds containing 1-hydroxy-2-oxo-1,8-naphthyridine moieties whose activity against HIV-1 integrase mutants confer resistance to currently approved INSTIs. These new compounds exhibit potent and selective activity against comprehensive and varied panels of INSTI-resistant mutants of HIV-1 integrase. Preliminary

rodent efficacy, metabolic, and pharmacokinetic studies have been completed by the NCI researchers.

The National Cancer Institute (NCI) seeks partners to in-license or co-develop this class of compounds for therapeutic use. Parties interested in licensing the technology should submit an Application for Licensing, and seek detailed information from the Licensing and Patenting Manager indicated below.

Co-development partners would apply under a Cooperative Research and Development (CRADA) to conduct pre-clinical studies that include lead optimization, *in vitro* and *in vivo* evaluation and preclinical development of a novel series of INSTIs for the treatment of infection by HIV-1 strains with resistance to currently available integrase inhibitors, including raltegravir and elvitegravir. Under the CRADA, further *in vitro* and *in vivo* ADME, as well as activity studies, will be conducted by the partner on current and optimized lead compounds using rodent and non-rodent models. Efficacy studies in non-human primates of select compounds are needed and will be part of the CRADA program. The CRADA scope will also include all aspects of toxicity studies, and synthesis scale up under GMP of optimized lead compounds to support submission of a successful IND application.

Interested potential CRADA collaborators can receive detailed information by contacting the Licensing and Patenting Manager (see below). Interested parties will receive detailed information on the current status of the project after signing a confidentiality disclosure agreement (CDA) with NCI. Interested candidate partners must submit a statement of interest and capability to the NCI point of contact for consideration by 5:00pm Eastern Standard Time, December 30, 2016.

Guidelines for the preparation of a full CRADA proposal will be communicated to all respondents with whom initial confidential discussions have been established. Licensing of background technology related to this CRADA opportunity is also available to potential collaborators. All proposals received by the above date will be considered. NCI reserves the right to consider additional proposals or none at all if no partner is selected from the initial response.

POTENTIAL COMMERCIAL APPLICATIONS

- HIV therapeutic for drug-resistant compounds of HIV-1 integrase

COMPETITIVE ADVANTAGES

- Currently, the only INSTI effective against drug resistant mutants of HIV-1 integrase

INVENTOR(S)

Terrence Burke, Stephen Hughes, Yves Pommier, Xue Zhao, Mathieu Metifiot, Stephen Smith, Barry Johnson, Christophe Marchand (all from NCI)

DEVELOPMENT STAGE

- Pre-clinical (in vivo)

PUBLICATIONS

- Zhao, X.Z. *et al.*, ACS Chem Biol., Apr 15, 2016, 11(4):1074-81. PMID: [26808478](#)
- Métifiot, M. *et al.*, Nucleic Acids Res., Aug 19, 2016, 44(14):6896-906. PMID: [27369381](#)
- Zhao, X. Z. *et al.*, *J. Med. Chem.*, 57, 5190-5202 (2014).
- Zhao, X. Z. *et al.*, *J. Med. Chem.*, 57, 1573-1582 (2014).

PATENT STATUS

- **U.S. Provisional:** US Provisional App. No.: 61/952,928 filed May 16, 2013
- **U.S. Provisional:** US Provisional App. No.: 61/899,061 filed November 1, 2013
- **U.S. Filed:** US Non-Provisional App. No.: 14/891,309 filed May 13, 2014
- **Foreign Filed:** Applications filed in Brazil, Canada, China, Europe, India, Japan, and South Africa

THERAPEUTIC AREA

- Infectious Diseases